REMARKS

Claims 11-42, 63, 65-86, 88-89, 94-101 and 106-108 are pending in this application. Claims 11-42, 65-70, 73, 76-82, 85, and 88-89 have been withdrawn from consideration as nonelected subject matter. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101, and 106-108 that read on the species "Amb a1" as the specific antigen and the sequence "AACGTTCG" as a specific ISS are being acted upon by the Examiner. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101, and 106-108 were variously rejected under 35 U.S.C. §112, first paragraph. Claims 71, 83, 96, and 100 were rejected under 35 U.S.C. §112, second paragraph. Claims 63, 71, and 94 were rejected under 35 U.S.C. §102(b). Claims 63, 71, 72, 75, 83, 84, 86, 94-101, 106, and 107 were variously rejected under 35 U.S.C. §103.

By this amendment, claims 94 and 98 have been canceled, claims 63, 75, 95-97, 99-101, and 106-108 have been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were rejected for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were rejected as allegedly containing subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Claims 63, 71, 72, 74, 75, 83, 84, 86, 94-101 and 106-108 were rejected for allegedly containing new matter. Applicants respectfully traverse these rejections.

As an initial matter, the Office states that the term "comprises" "expands the immunostimulatory stimulatory sequence (ISS) to include additional undisclosed nucleotides at either end or both ends so long the nucleotide sequence has a 5' cytosine and a 3' guanine." Office Action, page 4. Applicants would like to make clear that the claimed invention is directed to ISS which comprise "5'-cytosine guanine-3'." The term "5'-cytosine guanine-3' " indicates that the ISS includes a CG dinucleotide in which the C is to the 5' side of the G and the G is to the 3' side of the C. This terminology is clear in the specification and well-known to those of skill in the art. For example, all of the exemplary ISS listed on page 36-38 of the specification contain a CG dinucleotide and none of them contain a C on the 5' end of the oligonucleotide and a G on the 3' end of the oligonucleotide. As described and exemplified, the ISS may include additional bases on either side of the CG. Further, the same 5'-CG-3' or CpG terminology is used in the same way in all of the references regarding immunostimulatory nucleic acid cited by the Office. Thus, the Office's characterization of an oligonucleotide comprising a 5'-CG-3' as one which has a C on the 5' end of the oligonucleotide and a G on the 3' end of the oligonucleotide is incorrect. The claimed invention is directed to the use of an ISS comprising a 5'-cytosine guanine-3', i.e., an ISS which includes a CG dinucleotide sequence.

Enablement

As amended herein, the claimed invention is directed to populations of ISS-allergen conjugate molecules. Allergens for use in the claimed invention are well known in the art. Polynucleotides greater than 8 and less than about 200 nucleotides in length comprising an ISS, wherein the ISS comprises a CG dinucleotide, are also well known in the art. The invention lies in the unique combination and resultant activity of the ISS-allergen conjugate molecules prepared according to the instant specification.

Oligonucleotides comprising ISS for use in the present invention are described in the specification and well known in the art. Pages 36-43 of the specification provide over 75 examples of ISS for use in the invention, as well as methods for making additional ISS-containing polynucleotides. At pages 66-69, the specification provides methods by which the skilled artisan can assess the activity of any ISS-containing polynucleotide. Applicants also submit that ISS comprising a CG dinucleotide were well known in the art at the time the application was filed and that the relative level of skill in the art is high. A review of the many references regarding CG-containing immunostimulatory sequences cited in the specification and submitted to the Office clearly shows that a CG dinucleotide is a necessary element of the claimed category of immunostimulatory sequences. The specification also provides many examples of well-known allergens for use in the claimed invention. See, for example, the allergens and citations listed in Table 1, pages 44-47. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The court in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. "Since one embodiment is ... disclosed in the specification, along with the general manner in which its current range was ascertained, ... other permutations of the invention could be practiced by those skilled in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d. 788, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); MPEP §2164.04.

The Examiner states that the specification is enabling for a population of conjugate molecules comprising a ragweed pollen allergen Amb a1 and an immunostimulatory sequence (ISS) consisting of a sequence selected from the group consisting of SEQ ID NO:1-8. The Examiner also

states that the specification does not reasonably provide enablement for any ISS comprising the sequence 5'-CG-3' or for any ISS comprising the sequence 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3'. Office Action, page 3. The Examiner then concludes that "it would require undue experimentation even for one skilled in the art to practice the claimed invention." Office Action, page 6.

The Examiner points to the Stryer, Ngo, and Chatel references[1] as supporting that "there is insufficient guidance as to the structure of the "antigen" and "mammal antigen" without the amino acid sequence." Office Action, page 4. The Examiner states that Stryer teaches that "a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein." The Examiner also supports this rejection by stating that Ngo teaches "that the amino acid positions within the polypeptide/protein that can tolerate change ... which are critical to maintain the protein's structure/function will require guidance." The Examiner states that Chatel teaches "various factors such as antigen or allergen structure, mouse strain, CpG/recombinant protein expression influence the immune response." Office Action, pages 4-5. The Ngo reference pages cited by the Examiner discuss algorithms for predicting structure of a given protein from its amino acid sequence, the Stryer reference pages cited by the Examiner discuss the basic levels of protein structure, and the Chatel reference discusses genetic immunization using plasmid DNA.

Not one of these references, however, provides evidence to support the assertion that the specification does not enable one of skill in the art to make and use the claimed compositions. As described in the specification, allergens are well known in the art and Applicants respectfully submit that specification as filed fully enables the use of allergens in the claimed compositions.

[1] Stryer et al. (1988, Biochemistry, pp. 31-33; "Stryer"), Ngo et al. (1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495; "Ngo"), and Chatel et al. (2003, Allergy 58:641-647; "Chatel"), all cited in Office Action.

The Examiner again points to the Van Uden, Segal and Yamada references[2] to support the lack of enablement rejection. However, for reasons already of record, these references do not support a state of the art such that the claimed invention is not enabled.

Applicants respectfully submit that none of the cited references, when taken in its entirety, support the alleged state of unpredictability with regard to the claimed invention and thus, do not provide acceptable documentation or sound scientific reasoning to support any doubt of the teachings of the specification. See, for example, *In re Marzocchi*, 439 F2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Unless such documentation and/or scientific reasoning are adduced, the statements made in the specification are to be taken at face value. Thus, Applicants respectfully submit that a *prima facie* case for lack of enablement has not been established and that the claimed invention is enabled by the specification.

Fulfillment of the enablement requirement does not require that every embodiment of the invention be predictable. Rather, unpredictability is permitted, the level of unpredictability permitted depending on the level of guidance provided by the specification and the knowledge in the art. Applicants respectfully note that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands*, *Supra*, (Fed. Cir. 1988). Applicants respectfully submit that the specification has provided a reasonable amount of guidance to the skilled artisan with respect to both allergens and of ISS-containing polynucleotides and that the skilled artisan would be able to extend the teachings of the specification and the art to the compositions as claimed.

Thus, Applicants respectfully submit that a *prima facie* case of lack of enablement has not been established. Accordingly, the pending claims are in compliance with the enablement requirements.

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[2] Van Uden et al. (1999, *J. Allergy Clin. Immunol.* 104:902-910, "Van Uden"), Segal et al. (2000, *J. Immunol.* 164:5683-5688, "Segal"), Yamada et al. (2002, *J. Immunol.* 169:5590-5594, "Yamada"), all cited in Office Action.

Written Description

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

The Examiner asserts that the specification does not reasonably provide a written description of any ISS comprising the sequence 5'-CG-3' or of any antigen and states that "one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus." Office Action, pages 9 and 13. The Examiner asserts that written description requires "the sequence itself." In support, *Fiers v. Revel*, 25 USPQ2d 1601 (Fed. Cir. 1993), *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), and *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) are cited.

Applicants submit that the written description standard used by the Examiner for this rejection is not appropriate for the nature of the present invention. The cited decisions are directed to nucleic acid sequences which encode specific polypeptides and, thus, sequences encoding the functional polypeptide were required for enablement of the invention. These decisions are not applicable to the facts of the present invention. The present invention involves the use of an ISS which relies on the presence of the 5'-CG-3' dinucleotide for activity. Many sequences which include the 5'-CG-3' sequence as well as additional nucleotide bases are known to provide immunostimulatory activity to the ISS-containing polynucleotide are described in the specification and are known to those of skill in the art, as discussed herein.

As amended, claims 63, 75 and 108 are directed to populations of conjugate molecules involving an allergen. The specification lists many examples of well-known allergens for use in the claimed invention. Although not explicitly presented in the specification, specific information for the allergens, including structural information, was well known in the art at the time the application

was filed. See, for example, the allergens and citations listed in Table 1, pages 44-47. All of these references were published prior to the priority date of the present invention. Thus, much information about allergens, including amino acid sequence information, was known in the art at the time of filing. Applicants respectfully submit that the specification in combination with that known in the art adequately describes possession of the claimed genus "allergen" to one skilled in the art.

Quoting from the Office's Written Description Requirement Guidelines, the court in *Enzo* stated that "the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added)." *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

Applicants respectfully submit that the specification in combination with that known in the art provides a description of sufficient, relevant, identifying structural and functional characteristics of ISS-containing polynucleotide and allergen of the conjugates molecules to adequately describe possession of the claimed genus to one skilled in the art. Thus, the pending claims are fully described in the specification as filed. Accordingly, Applicants respectfully submit that the written description requirement has been met.

New Matter

The Examiner asserts that the "specification discloses only "greater than 8 and less than about 200 nucleotides" on page 43, line 1-3." Office Action, page 13. Applicants respectfully disagree with this assertion. In the cited section, the specification provides non-limiting examples of lengths for ISS-containing polynucleotides of the invention. Certainly, the specification does not disclose only polynucleotide lengths "greater than 8 and less than 200 nucleotides." This notwithstanding, Applicants have amended claims 63, 75, and 108 solely in an attempt to expedite prosecution of this application. Accordingly, the pending claims are in compliance with the new matter requirement.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 71, 83, 96, and 100 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

With regard to claims 71 and 83, the Examiner states that "claim 63 recites "...ISS comprises 5'-cytosine, guanine-3'..." but "does not recite the "5'-cytosine, guanine-3" is the CG dinucleotide with the ISS as argued." The Examiner states that "[c]laim 63 as written refers to ISS having a sequence begins with 5' cytosine (c) and ends with Guanine (G) at the 3' end instead of 5' purine, purine (i.e. A or G), C, G, pyrimidine, pyrimidine, C, G-3' is dependent claim 83 [sic]." Office Action, page 15.

For reasons already of record, Applicants maintain that the Examiner's interpretation of the language of claims 63 and 75 is incorrect and inconsistent with that taught in the specification and in the art, including all of the art cited by the Examiner in this case. The specification makes clear that the phrase "ISS comprises the sequence 5'-cytosine, guanine-3' is the same as "ISS comprises a CG dinucleotide" or "ISS comprises 5'-cytosine guanine-3'." Again, Applicants direct attention to the over 75 exemplary ISS for use in the invention listed on pages 36-37, all of which include at least one "cytosine guanine" (CG) and none of which have a C on the 5' end and a G on the 3' end.

For these reasons, Applicants believe that the claims were sufficiently definite. This notwithstanding, Applicants have amended claims 63 and 75 solely in an attempt to expedite prosecution of this application.

In view of the proper interpretation of the pending claims, Applicants respectfully point out that the ISS recited in claims 71 and 83, i.e., 5'-purine, purine, C, G, pyrimidine, pyrimidine, C, G-3', includes the ISS recited in claim 63 and 75, i.e., 5'-cytosine guanine-3', plus additional nucleotides. Since claims 63 and 75 use comprising language with the ISS sequence, dependent claims 71 and 83 have proper antecedent support in independent claims 63 and 75, respectively.

With regard to claims 96 and 100, Applicants respectfully submit that the term "mammal allergen" is not ambiguous or indefinite. The specification provides a description of a variety of allergens for use in the invention at pages 43-47. In Table 1 in this section, the allergens are grouped according to source. For example, "fungal allergens" are allergens produced by fungi and "insect allergens" are those produced by insects. Accordingly, "mammal allergens" are those produced by mammals and examples of such are listed on page 41. Accordingly, the term "mammal allergen" is sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 63, 71, and 94 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Klinman *et al.* (1999, *Vaccine* 17:19-25; "Klinman"). Since the present application claims priority to U.S. provisional application No. 60/165,467, filed November 15, 1999, Applicants respectfully point out that if Klinman is to be cited, it should be done under 35 U.S.C. §102(a) rather than 35 U.S.C. §102(b). In any event, Applicants respectfully traverse this rejection.

The invention is based on the discovery that the ratio of ISS to antigen in a conjugate molecule can alter the immunostimulatory and biological activities of the conjugate molecule. For example, as the ratio of ISS to antigen in conjugate molecules increases for a population of conjugate molecules, the allergenicity of the molecules decreases, as does the ability of the molecules to stimulate antibody production. Thus, as amended, the claimed invention is directed to

a population of ISS-allergen conjugate molecules with particular activities. The invention lies in the unique combination and resultant activity of the ISS-allergen conjugate molecules prepared according to the instant specification. Claim 63 is directed to a population of conjugate molecules where the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per allergen molecule. Both structural and functional features of the claimed conjugate molecules are characterized and quantitated.

Klinman describes formation and use of a complex containing antigens and CG-containing oligonucleotides. The complexes are generated by crosslinking biotinylated oligonucleotide and biotinylated antigen with excess streptavidin. This process allows for the formation of a wide variety of complexes. Klinman provides no physical characterization of the resultant crosslinked complexes. There is no way for one to know whether the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule as claimed.

The Federal Circuit has held that the "fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the references, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 49 USPQ2d 1949,1950-51 (Fed. Cir. 1999); MPEP §2112.

Klinman does test the conjugates for activity in generating antigen-specific antibodies. The Examiner states that Klinman teaches that "conjugates such as CpG oligo-avidin-OVA extremely immunogenic and at optimal CpG oligo mass:OVA ratios, IgG antibody production increased tenfold over OVA-avidin or OVA alone." Office Action, page 16. The showing that the optimal conjugates of Klinman result in increased antibody production does not support the assertion that Klinman inherently describes the claimed complexes. As noted above, the complexes of the claimed invention have a reduced ability to stimulate antibody production as compared to

those with lower ISS:antigen ratios. Klinman does not explicitly or inherently teach the claimed invention and, thus, does not anticipate the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

Rejection under 35 U.S.C. §103

Claims 75 and 83 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Klinman. Claims 63, 71, 72, 75, 83, 84, 86, 94-101, 106, and 107 were rejected under 35 U.S.C. §103 as allegedly unpatentable over Klinman in view of WO 98/16247 ("Carson"). Applicants respectfully traverse these rejections.

Claims 75 and 83 over Klinman

A *prima facie* case of obviousness requires the satisfaction of three requirements. First, as in this case only a single, non-anticipatory document is cited, the reference must suggest all of the claim limitations. Second, the reference must provide a suggestion or motivation to modify the teachings either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. Third, the reference must provide a reasonable expectation of success. MPEP §2143.

More specifically, the obviousness analysis under 35 U.S.C. §103 requires the consideration of the scope and content of the prior art, the level of skill in the relevant art, and the differences between the prior art and the claimed subject matter. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Critical elements of the invention as a whole which clearly distinguish the entire invention from the prior art references cannot be ignored. *Panduit Corp. v. Dennison Manufacturing Co.*, 1 USPQ2d 1593, 1597 (Fed. Cir.), *cert. denied*, 481 U.S. 1052 (1987). Any disclosure teaching away from the claimed invention also must be considered in the obviousness analysis. MPEP §2142.01. The fact that a disclosure can be modified is insufficient to establish *prima facie* obviousness in the absence of a suggestion or motivation to make such a modification. *Id.* Simply stated, the suggestion or motivation to modify a reference must be found in the prior art.

Claims 75 and 83 are directed to a population of conjugate molecules where the extent of conjugation in the population provides a ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of allergen of at least about 45 to about 40. Therefore, a *prima facie* case of obviousness requires that the cited reference or the art suggest the claimed population of conjugates molecules. Klinman or the general knowledge of the art must provide a motivation to modify the teachings therein to result in the claimed composition and must provide a reasonable expectation of success in modifying the teachings therein. For the reasons discussed below, the cited reference fails to fulfill these requirements for *prima facie* obviousness.

As discussed herein, Klinman discloses cross-linked complexes containing antigens and CG-containing oligonucleotides. The Examiner acknowledges that Klinman differs from the claimed invention in the extent of conjugation in the population. Office Action, page 16. Applicants respectfully submit that Klinman does not suggest the claimed population of conjugate molecules because the reference is completely silent on any desirability to modify the complexes taught therein to those claimed.

The Examiner asserts that it "would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the ratio of average mass of ISS-containing polynucleotide to average mass of antigen for a population of conjugate molecules comprising any antigen and polynucleotide comprising ISS." Office Action, page 17. Applicants disagree with this assertion and submit that Klinman's silence regarding to the ratio of average mass of polynucleotide to average mass of antigen and the claimed extent of conjugation provides no suggestion or motivation to modify the teaching therein to the arrive at the claimed conjugate population.

The Examiner states that "it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art." Office Action, page 17. However, in the description of "Obviousness of Ranges," MPEP §2144.05 II.B. sets forth the standard that "Only Result-Effective Variables Can Be Optimized." That subsection states as follows:

> "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation."

Klinman does not teach that the ratio of ISS to antigen as claimed is a result-effective variable. Klinman provides not indication that varying the ratio of ISS to antigen in a conjugate molecule can alter the immunostimulatory and biological activities of the conjugate molecule. Accordingly, optimization of the ratio of ISS to antigen to achieve a particular activity is not *prima facie* obvious.

In contrast to Klinman, the present invention provides a population of conjugate molecules where the particular ratio of ISS to antigen decreases the ability of the molecules to stimulate antibody production and decreases the allergenicity of the molecules. Neither Klinman nor knowledge in the art provides any suggestion or motivation to modify the teaching of Klinman to arrive at the claimed invention.

Finally, Klinman does not provide a reasonable expectation of success of the claimed invention. Since Klinman is silent with regard to the claimed population of conjugate molecules, it is impossible for the cited reference to convey a reasonable expectation of success.

Accordingly, Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Claims 63, 71, 72, 75, 83, 84, 86, 94-101, 106, and 107 over Klinman with Carson

A *prima facie* case of obviousness requires that three basic criteria must be met. First, as in this case two documents are cited, the references when combined must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the

reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143.

More specifically, a *prima facie* case of obviousness requires that the Klinman and Carson must teach or suggest the claimed population of conjugates molecules. Klinman, Carson or the general knowledge of the art must provide a motivation to modify the teachings of Klinman and Carson to result in the claimed composition and must provide a reasonable expectation of success in modifying the teachings therein. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established. For the reasons discussed below, the cited references fail to fulfill these requirements for *prima facie* obviousness.

As discussed herein, Klinman does not explicitly or inherently teach or suggest the claimed invention. Carson describes conjugate molecules comprising an immunostimulatory oligonucleotide and an antigen, including an allergen. The Examiner states that the conjugate molecules of Carson "boost the host's immune response toward a Th1 phenotype to avoids the risk of immunization induced anaphylaxis." Office Action, page 18. Carson, however, does not supply what is missing from Klinman. Carson does not teach or suggest populations of conjugate molecules as claimed, i.e., where the extent of conjugation in the population provides an average of at least 5.5 ISS-containing polynucleotides per allergen or to where the extent of conjugation in the population provides a ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of allergen of at least about 45 to about 40. Thus, the combination of the two documents does not teach or suggest the claimed population of conjugate molecules.

Further, the cited references do not provide any motivation to modify the teachings therein to arrive at the claimed invention. Also, since the cited references are silent with regard to the claimed population of conjugate molecules, it is impossible for the cited references to convey a reasonable expectation of success.

Thus, a *prima facie* case of obviousness has not been established.

In sum, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §103.

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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